REMARKS/ARGUMENTS

By this Amendment, the specification is amended, claim 58 has been canceled, claims 38, 45, 55, 61 are amended. Claims 46-48, 50, 66-71, 74 have been withdrawn from consideration pursuant to a restriction requirement. Claims 38-57, 59-74 are pending, claims 38-45, 49, 51-57, 59-65, 72, 73 are under consideration.

Citations to the Specification are directed to U.S. Patent Application Publication No. 2004/0265350.

Support for the amendments to the claims can be found throughout the Specification as filed, and specifically: support for the amendment to claim 38 for the limitations wherein the carrier comprises block hydroxyapatite and that the density of the carrier is less than about 30% theoretical can be found in paragraphs [0032], [0058], [0062], and [0064].

Applicants hereby affirm their prior election with traverse of Group I, claims 38 to 73, and further elected the species chemotherapeutic agents, specifically MTX, reserving their rights under 35 USC § 121 to file a divisional application for the nonelected claims.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Objection to the Specification

The Examiner objected to the Specification allegedly because the limitations of claims 38, 40, and 41, wherein the pores are in the range of about 20 to about 800 micron, or about 60 to about 800 micron, are not specifically recited in the specification. This objection is respectfully traversed. The specification has been amended to specifically recite the limitations of claims 38, 40 and 41, wherein the pores are in the range of about 20 to about 800 micron, or about 60 to

about 800 micron.

Additionally, the Examiner alleges that the limitation of claim 44 wherein the density ranges from about 10% to about 30% of theoretical density is not specifically recited in the specification as originally filed. This objection is respectfully traversed. The specification has also been amended to specifically recite the limitation of claim 44 wherein the density ranges from about 10% to 30% theoretical density.

Reconsideration and withdrawal of the objections to the Specification are respectfully requested.

Claim Objections

Claim 38 is objected to because the claim contains a typographical error wherein "Interconnected" appears, rather than "interconnected." In response, claim 38 has been amended to recite "interconnected". Reconsideration and withdrawal of the objection is respectfully requested.

Claim 55 is objected to because the Examiner alleges that the claim appears to be a Markush-type claim, but the support materials are not listed in the alternative. In response, claim 55 has been amended to recite "or". Reconsideration and withdrawal of the objection is respectfully requested.

Rejections under 35 USC 112 second paragraph

Claims 45 and 61 stand rejected under 35 U.S.C, 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, because the phrase "or the like" allegedly renders the claim(s)

indefinite. The rejection is traversed because the claims have been amended to remove the phrase "or the like". Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 55 stands rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed. Claim 55 has been amended to recite the chemical names as well as the abbreviations. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 58 is rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed. The claim has been canceled, therefor reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 USC § 102

Claims 38-45, 49, 59, 61, 62, 64, 65, 72, and 73 stand rejected under 35 U.S.C. 102(b) as being anticipated by Itokazu et al. (J. Biomed. Mater. Res., 1998, 39, p. 536 - 538). This rejection is respectfully traversed.

In Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the Itokazu reference.

The Examiner argues that Itokazu teaches porous apatite ceramics (PAC), including ß-

tricalcium phosphate (TCP), which have a porosity of 75 - 80% and pore size range of 100 - 400 μm for the sustained release of a chemotherapeutic, methotrexate (MTX). The Examiner further alleges that a ceramic with a porosity of 75 - 80% would inherently have a theoretical density of 20 - 25%, and that the MTX was loaded into the pores of the ceramic carrier via centrifugation, and that the TCP is resorbable.

However, while Itokazu teaches the loading of a chemotherapeutic agent, MTX, into the pores of a porous apatite ceramic, only experiments with two types of porous apatite ceramic are discussed: hydroxyapatite block having a porosity of 35-48% and a pore size range of 50-300 μm; and ß-tricalcium phosphate block having a porosity of 75-80% and pore size range of 100-400 μm. In contrast, amended claim 38 requires a ceramic carrier comprising hydroxyapatite block having a density of less than 30% theoretical, i.e. a porosity of more than 70%. Hence, amended claim 38, and the claims dependent therefrom, are not anticipated by the disclosure of Itokazu, because Itokazu does not disclose each and every feature of the claim (i.e. a ceramic carrier comprising hydroxyapatite block having a density of less than 30% theoretical).

Accordingly, reconsideration and withdrawal of the rejection of claims 38-45, 49, 59, 61, 62, 64, 65, 72, and 73 under 35 USC 102(b) is respectfully requested.

Claims 38 - 44, 51, 52, 61, 63, 72, and 73 stand rejected under 35 U.S.C. 102(e) as being anticipated by Imura et al. (US 6,340,648). This rejection is respectfully traversed.

Here, not every element of the claims is present in the Imura reference. The Examiner

alleges that Imura teaches a calcium phosphate porous sintered body which comprises spherical pores communicating with one another substantially throughout the body, and with a porosity between 55 - 90% (i .e. a theoretical density of 10 - 45%). The Examiner further alleges that Imura discloses that the pore diameter is preferably 200 - 5000 μm, that the device may be a carrier for drug delivery and gradual release, and that medicine for promoting osteogenesis (or another medicament) may be included within the pores.

However, while Imura discloses calcium phosphate porous sintered bodies with a porosity of 55-90%, as regards hydroxyapatite bodies it discloses only articles having porosities of 65% (Example 3), 68% (Example 4) and 70% (Examples 1 and 2). This is outside the range required by amended claim 38, i.e. less than 30% theoretical density. Consequently, amended claim 38 and the claims dependent therefrom are novel over the disclosure of Imura.

Accordingly, reconsideration and withdrawal of the rejection of claims 38 - 44, 51, 52, 61, 63, 72, and 73 under 35 USC 102(e) is respectfully requested.

Claims 38 - 45, 59 - 61, 72, and 73 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hakamatsuka et al. (US 5,318,779). This rejection is respectfully traversed.

Here, not every element of the claims is present in the Hakamatsuka reference. The Examiner alleges that Hakamatsuka teaches a drug-impregnated ceramic to be embedded in a living body, and that the porous ceramic has pores with a size of 10 - 300 μm, a drug impregnating the ceramic pores, and a surface layer for controlling the release of the drug. The Examiner further alleges that Hakamatsuka teaches that the porous ceramic is formed of

tricalcium phosphate (TCP), which is adsorbed by a living body, that the porosity of the ceramic may be 70% (i.e. the ceramic may have a density of 30% of theoretical) and that the surface layer consists of collagen having a 10 μm pore size and a thickness of 300 μm (i.e. a biodegradable polymer).

However, while Hakamatsuka discloses a drug-impregnated ceramic to be embedded in a living body, the drug-impregnated ceramic of Hakamatsuka includes a porous ceramic, preferably comprising tricalcium phosphate having pores with a pore size of 10 to 300 μm and a surface layer for controlling the release of the drug covering at least a portion of the outer surface of the porous ceramic and has a porosity lower than that of the porous ceramic. Hakamatsuka teaches that the pore size of the surface layer is preferably less than 10 μm and its thickness is 300 μm or less. Thus, Hakamatsuka discloses drug-impregnated ceramics having a porosity of 30%, 50% and 70%, i.e. densities of 70%, 50% and 30% theoretical. Therefore, Hakamatsuka does not disclose a hydroxyapatite carrier having a density below 30% theoretical, as required by amended claim 38. Therefore, amended claim 38 and the claims dependent therefrom are novel over Hakamatsuka.

Accordingly, reconsideration and withdrawal of the rejection of claims 38 - 45, 59 - 61, 72, and 73 under 35 USC 102(b) is respectfully requested.

Claims 38 - 44, 53, 54, 61 - 63, 72, and 73 stand rejected under 35 U.S.C. 102(e) as being anticipated by Starling et al. (US 6,358,532). This rejection is respectfully traversed.

Here, not every element of the claims is present in the Starling reference. The Examiner

alleges that Starling discloses calcium phosphate-based microcarriers and their use as implantable biomedical materials, that the calcium phosphate may be hydroxyapatite, tricalcium phosphate, etc. The Examiner further alleges that Starling teaches that the density of the microcarrier may be from 25 - 75% of theoretical density, and the pore size is from 30 – 80 μm, and that a calcium phosphate microcarrier with open porosity can be used with collagen to form a composite implantable material.

However, while Starling discloses calcium phosphate-based microcarriers and microspheres and their use in a number of applications including implantable biomedical materials, Starling discloses the bonding of microspheres into an aggregate. Consequently, there would be another material, e.g. a cement, between the microcarriers. Therefore, the porosity of one microcarrier would not communicate with the porosity of its neighbors. This is in contrast to amended claim 38, which requires an interconnected skeleton comprising hydroxyapatite block. Hence, amended claim 38 and the claims dependent therefrom are novel over the disclosure of Starling.

Accordingly, reconsideration and withdrawal of the rejection of claims 38 - 44, 53, 54, 61 - 63, 72, and 73 under 35 USC 102(e) is respectfully requested.

* * *

Rejection under 35 USC 103

Claims 38 - 45, 49, 59, 61 - 65, 72, and 73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Itokazu et al. (J. Biomed. Mater. Res., 1998, 39, p. 536 - 538). This rejection is respectfully traversed.

The claims are patentable over the Itokazu reference for the following reasons. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), MPEP 2143.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). MPEP 2143.03.

In the instant case, not every element of the claims is taught or suggested in the Itokazu reference. The Examiner alleges that Itokazu teaches porous apatite ceramics (PAC), including ß-tricalcium phosphate, which have a porosity of 75 - 80% (i.e. a theoretical density of 20 - 25%) and pore size range of 100 - 400 μm for the sustained release of a chemotherapeutic, methotrexate (MTX), and that another porous apatite ceramic which is taught by Itokazu is calcium phosphate hydroxyapatite or HAb, which has a porosity of 35 - 48% (i.e. a theoretical density of 52 - 65%) and pore size of 50 – 300 μm (page 536). The Examiner admits that the

calcium phosphate hydroxyapatite ceramic taught by Itokazu does not have a theoretical density of less than 40% theoretical, but argues that it would have been obvious to one of ordinary skill in the art to utilize a calcium phosphate hydroxyapatite sample with a lower theoretical density (i.e. including less than 40% theoretical), similar to a theoretical density between 20 - 25% for the TCP sample also taught by Itokazu because the TCP released higher concentrations of MTX at a slower rate than the HAb, which was attributed to the higher porosity (or lower theoretical density) and larger pore size. The Examiner argues that one would have been motivated to adjust the porosity of samples of calcium phosphate hydroxyapatite to be similar to that of the TCP employed in the experiments of Itokazu (i.e. including less than 40% theoretical) in order to achieve a carrier with an optimal balance of a desirable MTX release profile and adequate mechanical strength.

However, while Itokazu teaches the loading of a chemotherapeutic agent, MTX, into the pores of a porous apatite ceramic, in the Itokazu reference experiments with two types of porous apatite ceramic are discussed: hydroxyapatite block having a porosity of 35-48% and a pore size range of 50-300 μm; and ß-tricalcium phosphate block having a porosity of 75-80% and pore size range of 100-400 μm. In contrast, amended claim 38 requires a ceramic carrier comprising hydroxyapatite block having a density of less than 30% theoretical, i.e. a porosity of more than 70%. Hence, amended claim 38 is not obvious over the disclosure of Itokazu, because Itokazu does not teach or suggest each and every feature of the claim (i.e. a ceramic carrier comprising hydroxyapatite block having a density of less than 30% theoretical), and does not provide motivation for one of skill in the art to adjust the adjust the porosity of samples of calcium

phosphate hydroxyapatite.

Accordingly, reconsideration and withdrawal of the rejection of claims 38 - 45, 49, 59, 61 - 65, 72, and 73 under 35 USC 103(a) is respectfully requested.

Claims 38 – 45, 49, 53, 54, 56 – 57, 59, 61 - 65, 72, and 73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Genin (US 6,767,550) in view of Itokazu et al. (J. Biomed. Mater. Res.. 1998. 39, p. 536 - 538). This rejection is respectfully traversed.

Here, not every element of the claims is taught or suggested in the combination of the Genin and Itokazu references. The Examiner alleges that Genin teaches a hydroxyapatite based drug delivery implant for cancer treatment, and that the ceramic component of the implant may be tricalcium phosphate, hydroxyapatite, etc. The Examiner admits that Genin fails to identify the specific density of the ceramic used in the porous ceramic implant. Thus, the Genin reference does not teach that the anti-cancer drug delivery device has a density which is specifically less than 40% theoretical, but the Examiner further alleges that Itokazu teaches porous apatite ceramics (PAC), including ß-tricalcium phosphate and hydroxyapatite, which may have a porosity of 75 - 80% (i.e. a theoretical density of 20 - 25%), and pore size range of 100 - 400 μm for the sustained release of a chemotherapeutic agent. The Examiner argues that it would have been obvious to one of ordinary skill in the art to utilize a ceramic with a density of less than 40% theoretical in the drug delivery implant of Genin consisting of drug-containing and drug-free layers because Itokazu demonstrated successful modified release of an anticancer agent via a similar ceramic with a theoretical density of 20 - 25%. The Examiner argues that the

motivation is in preparing a ceramic with a desired release profile, because Genin specifically teaches that modification of the microstructure, morphology, and composition of the bioresorbable material (i.e. ceramic or polymer) allows for control of the drug release profile.

However, while Genin discloses a drug delivery implant for cancer treatment, the implant is hydroxyapatite based and offers sustained drug release after implantation at a targeted site, Genin is silent with regard to porosities or pore sizes for controlling release rates. Consequently, Genin would not provide adequate instruction to the person skilled in the art regarding the use of sintered porous ceramics with controlled porosity and pore size. Nevertheless, the person skilled in the art using the Itokazu reference to modify the teaching of Genin, as the examiner suggests, would not arrive at an article having each and every feature required by amended claim 38, because (as discussed above) Itokazu does not teach or suggest hydroxyapatite block carriers having the density (less than 30% theoretical) required by amended claim 38. Therefore, the combination of the Genin reference and the Itokazu references does not teach or suggest every limitation of the claims.

Accordingly, reconsideration and withdrawal of the rejection of claims 38 – 45, 49, 53, 54, 56 – 57, 59, 61 - 65, 72, and 73 under 35 USC 103(a) is respectfully requested.

Claims 38 - 45, 49, 53 - 55, 59, 61 - 64, 72, and 73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bohner et al. (J. Pharm. Sci., 1997,86, p. 565 - 572) in view of Itokazu et al. (J. Biomed. Mater. Res., 1998, 39, p. 536 - 538). This rejection is respectfully traversed.

Here, not every element of the claims is taught or suggested in the combination of the Bohner and Itokazu references. The Examiner argues that Bohner teaches calcium phosphate cement of tricalcium phosphate and monocalcium phosphate hydrate as a delivery system for the antibiotic gentamicin sulfate. The calcium phosphate carrier may have a porosity of 70% (i.e. a density of 30% theoretical). Polyacrylic acid was added to the carrier as a release-modifier. The Examiner admits that Bohner fails to identify the size of the pores within the calcium phosphate. Thus, the Bohner reference does not teach a drug delivery device having pores which are in the range of 20 - 800 micron. The Examiner argues that it would have been obvious to one of ordinary skill in the art to use a calcium triphosphate ceramic with pores which are in the range of 20 - 800 micron in the calcium phosphate/PAA drug delivery device taught by Bohner because Itokazu teaches a similar calcium phosphate material having similar porosity (i.e. 75%) and a pore size of 100 - 400 μm to be an effective sustained-release drug delivery device for implantation into bone. The Examiner argues that the motivation is to obtain a carrier with a desired drug release profile.

However, Bohner teaches the use of an hydraulic calcium phosphate cement made of ß-tricalcium phosphate, monocalcium phosphate monohydrate and water as a delivery system for the antibiotic genanicin sulphate. The antibiotic is mixed into the cement as either a powder or an aqueous solution to concentrations of antibiotic solution of between 0 and 16% w/w of the total mass of ß-tricalcium phosphate and monocalcium phosphate monohydrate. Bohner describes sustained release by diffusion of the antibiotic from the cement, the rate of which is related to the porosity of the cement. Initial cement porosities of 38% and 69% were investigated

in the Bohner reference. Hence, having regard to the requirements of amended claim 38, Bohner does not disclose hydroxyapatite block having a density of less than 30% theoretical. Itokazu provides no teaching or suggestion to modify the Bohner reference by using hydroxyapatite block. Moreover, the disclosure of Itokazu in relation to hydroxyapatite block does not disclose or suggest amended claim 38 (as discussed above). Therefore the person skilled in the art combining the teaching of Bohner and Itokazu as the examiner suggests would not obtain an article having each and every feature required by amended claim 38, and the claims dependent therefrom.

Accordingly, reconsideration and withdrawal of the rejection of claims 38 - 45, 49, 53 - 55, 59, 61 - 64, 72, and 73 under 35 USC 103(a) is respectfully requested.

* * *

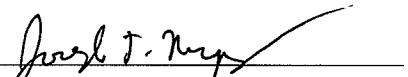
For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

May 29, 2007

By 
Joseph F. Murphy
Registration No. 58,313
Customer No. 03000
(215) 567-2010
Attorneys for Applicants

Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.